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EXAMINER

STAPLES, MARK

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/813,506	Applicant(s) SHOEMAKER ET AL.	
	Examiner MARK STAPLES	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 122, 178 and 185-232 is/are pending in the application.
- 4a) Of the above claim(s) 178, 186-188, 190, 191, 193-196, 198, 199, 201-220, 225 and 227 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 122, 185, 189, 192, 197, 200, 221-224, 226 and 228-232 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment of claims 202, 203, 206, and 228 in the paper filed on 09/10/2009 is acknowledged.

Claims 122, 185, 189, 192, 197, 200, 221-224, 226 and 228-232 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

2. The rejection of claims 228-231 under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (1997, previously cited), Bowtell (1999 previously cited), Hui et al. (United States Patent 6,013,436 filed August 19, 1996 and issued January 11, 2000), and Ashe et al. (1997) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment to claim 228.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 103

3. The rejection of claims 122, 185, 189, 192, 197, 200, 221-224, 226, and 232 under 35 U.S.C. 103(a) is maintained. The rejections are given below. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that although Hui et al. and Ashe et al. teach intron probes for detection of nucleic acids that one of ordinary skill in the art would not have been motivated to combine these teachings with those of Bowtell to arrive at the claimed microarray having at least two intron probes; as Applicant asserts that this would then be an array targeted to different materials. However and as cited, Ashe et al. specifically teach that it is desirable to use probes, including intron probes, to different materials by teaching: “**Double-label** primary transcript in situ hybridization was performed with [the material being] **gene-specific intron probes** (Wijgerde et al. 1995) and **a probe specific** to either the [materials being] **human LCR** or **Gg-globin 38-flanking region**” (see the 1st sentence of the 3rd paragraph on p. 2408). Thus Ashe et al. provide even further motivation to use probes to different materials in the arrays of Bowtell who teaches probe detection of sequences for protein expression: as Ashe et al. teach that it is desirable to detect nucleic acids which yield information about protein expression and at the same time to detect nucleic acids which do not yield information about protein expression.

Applicant presents the same argument for the teachings of Lockhart, i.e., that Lockhart only teaches coding sequences and does not specifically teach non-coding

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sequences. However as given above, Ashe et al. teach that it is desirable to simultaneously detect both coding and non-coding sequences with probes.

Applicant further argues that one of ordinary skill in the art would not have been motivated to apply the teachings of *in situ* hybridization of cell DNA or RNA to *in vitro* hybridization of cellular RNA or DNA on arrays of microarrays. However, Bowtell specifically teaches: "RNA preparation from cell lines is simple and straightforward" (see the 1st sentence of the 3rd paragraph on p. 25). Thus one of ordinary skill in the art would have known how to obtain the nucleic acids as taught by Ashe et al. and Hui et al. for hybridization on arrays. Bowtell provides the motivation to do this by teaching: "The use of DNA microarrays for comprehensive RNA expression analysis has caused a great deal of interest recently, although the concept is not new" and " . . . a general appreciation of the need to integrate information obtained from more traditional and reductionist approaches to biology make microarray- based expression analysis a powerful tool" (see the 1st paragraph of the body of text on p. 25).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation or some reason to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) and see the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, Bd. Pat. App. & Interf. June

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25, 2007 which cites *KSR*, 82 USPQ2d at 1396, available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

In this case, Hui et al. teach arrays for gene detection and gene structure with exclusively intron probes and other probes including probes to exons (see claim 23), and Lockhart et al. and Bowtell et al. also teach arrays of multiple and different probes for gene detection and gene structure. Hui et al. specifically teach the advantages of intron probes. Thus it would have been obvious to one of ordinary skill in the art to combine the intron probes with those of Lockhart et al. and Bowtell et al. to further enhance arrays for gene detection and gene structure. Examiner further cites Ashe et al. to demonstrate that the knowledge of intron probes was generally available to one of ordinary skill in the art, thus negating at least this part of Applicant's argument to the contrary. Furthermore, Ashe et al., as with the other cited prior art, teach that gene-specific intron probes can be used to detect a gene in a plasmid structure which is a type of gene structure. Thus the prior art teaches use of intron probes for gene detection and gene structure in arrays.

Applicant argues that Schena is only concerned with analysis of gene expression and argues that one of ordinary skill in the art would not have combined the teachings of Schena with the other cited prior art. However, as given above Hui et al. provide a motivation to use intron probes and Bowtell teaches that arrays are useful for detection of nucleic acids in general. Thus in view of the combined teachings, it would have been

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obvious from the combined teachings of the cited prior art to detect plant nucleic acid sequences with the claimed arrays

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 122, 185, 189, 192, 197, 200, 221, 222, 224, 226, and 232 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (1997, previously cited), Bowtell (1999 previously cited), Hui et al. (United States Patent 6,013,436 filed August 19, 1996 and issued January 11, 2000), and Ashe et al. (1997, previously cited).

Regarding claim 122 and 200, Lockhart et al. teach an array, comprising:

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a positionally-addressable ordered array of polynucleotide probes bound to a solid support (entire reference especially Figures 1-4 and column 23 line 28-29: "Probes may be laid out on an polynucleotide array with a specifically defined positional relationship");

and said polynucleotide probes comprising a plurality of at least 100 polynucleotide probes of different nucleotide sequences (entire reference especially Figures 1-4 and claim 1 "at least four hundred different polynucleotides sequences per square centimeter"), each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, said different genomic sequences being found at sequential sites in the genome of said species of organism (entire reference, especially Figure 2, Brief Description of the Figures, and SEQ ID NOS: 6-37 for the specie Homo Sapiens), wherein the distance between 5' ends of said sequential sites is always less than 500 bp (entire reference, especially "Single Increment Tiling" found in column 9 line 62 through column 10 line 7 in which each probe overlaps and where sequence signature includes nucleotide sequences at most 300, 250, 200, 150, 100, 75, 50, 30 , 25 or 15 nucleotides in length found in column 7 lines 36-38; and thus for overlapping sequences of 300 or less, the distance between 5' ends of any two sequential overlapping sites always must be less than 500 bp; as the maximum 5' distance end to end, which needs to include at least 1 overlapping nucleotide, is $300-1 = 299$ bp).

Although this is a new rejection it is noted that Applicant argues that Lockhart et al. teaches away from intron probes by teaching to avoid probing regions that are near

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intron/exon expected boundaries. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., intron/exon boundaries) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Since Lockhart et al. teach arrays for genes (see Abstract) and Ashe et al. also teach detection of genes using gene-specific intron probes specific (entire Article especially the last full paragraph on p. 2503 and Figure 9), it would have been obvious to use the intron probes of Ashe et al. in the arrays of Lockhart et al. for gene detection, as given more fully below.

Regarding claim 185, Lockhart et al. teach that a desired level of information may be determined, that is, that one can exclude low information content (see column 12 lines 7-10). As the specification does not provide a closed definition of "low information", this teaching of Lockhart et al. reads on the claim language.

Regarding claim 189, Lockhart et al. teach an array with probe density ranging from 625 to 10 million probes per 1 cm^2 and thus teach an array having greater than 50,000 different polynucleotide probes per 1 cm^2 . (col. 7, lines 1-9).

Regarding claim 192, Lockhart et al. teach an array where the sequences targeted by the probes are spaced apart by less than 200 bp (entire reference, especially "*Single Increment Tiling*" found in column 9 line 62 through column 10 line 7 in which each probe overlaps and where sequence signature include nucleotide

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sequences at most 300, 250, 200, 150, 100, 75, 50, 30, 25 or 15 nucleotides in length found in column 7 lines 36-38; and thus for overlapping sequences of 200 or less, the distance between 5' ends of any two sequential overlapping sites always must be less than 200 bp; as the maximum 5' distance end to end, which needs to include at least 1 overlapping nucleotide, is $200-1 = 199$ bp).

Regarding claim 197, Lockhart et al. teach an array wherein each nucleotide sequence of the array consist of 102-103 nucleotide sequences as given in SEQ ID NOS: 5-37 (See Figure 5 and 6, Sequence Listing, and description of Figures 5 and 6 found in column 6 lines 49-67).

Regarding claims 221, 222, and 224, Lockhart et al. teach wherein the organism is a human, *Homo Sapiens*, which is a mammal which is an eukaryote (see Sequence Listing for SEQ ID NOS: 5-27 where the organism is *Homo Sapiens*, Figure 5 and 6, Sequence Listing, and description of Figures 5 and 6 found in column 6 lines 49-67).

Regarding claim 226, Lockhart et al. teach an array with at least 10,000 probes by teaching high density arrays, with probe density ranging from 625 to 10 million probes per 1 cm^2 . (Fig. 2; col. 6, lines 62-67; col. 7).

Regarding claim 232, as Lockhart et al. teach excluding regions of low information content as given for claim 195 above, Lockhart et al. necessarily teach determining the distance with after excluding the regions of low information content.

Regarding claim 122, Lockhart et al. do not specifically teach an array wherein the genomic target sequences for a plurality of probes span a genomic region of at least 25,000 bp.

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Bowtell teaches microarrays having regions of 42,000 (42k) and 30,000 (30k) gene sets, each of which is over 25,000 bp and that the entire genome of *C. elegans* (entire reference, especially Table 3, 2nd column first two entries, p. 26 column 2 - 2nd paragraph, and supporting document, Human Genome Project, p. 3 chart showing 3 billion base for the human genome and 97 million bases for *C. elegans* genome).

Although this is a new rejection it is noted that Applicant argues that Bowtell deals solely with genes of protein expression and thus one would not combine these teachings with the teachings of Lockhart et al. However it is noted that even if the teachings of Bowtell are solely directed to protein expression by doing RNA expression analysis (see first sentence on p. 25), Lockhart et al. specifically teaches that their array based methods can include protein expression through RNA expression analysis and thus can include the probes of Bowtell (and of Hui et al. and Ashe et al. as given later):

“All of the methods discussed herein can include: correlating RNA levels with gene sequences of interest; the identification and use of expression patterns; and the narrowing of expression pattern information in a hierarchical fashion; or the selection, including by experimental design, of subsets of particular expression profiles. For example, one can look for the absence of sequence signatures of enzymes [a type of protein] involved in a particular metabolic pathway” (see column 1 lines 51-59); and

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“The hierarchical methods of the present invention are particularly useful in the identification of gene family members; the discovery of new gene family members or other molecules; the identification of nucleic acid fragments as being from or containing certain regions of a genome (human or otherwise) . . . ” (see column 14 lines 8-13).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the arrays which include protein expression detection through RNA expression analysis of Lockhart et al. by spanning genomes as suggested by Bowtell with probes which detect protein expression through RNA expression analysis with a reasonable expectation of success. The motivation to do so is provided by Bowtell who teach the usefulness of array to span genomes and the teaching of Lockhart et al. that array can span gene families (see Figure 3 and its description in column 5 lines 27-33) and in view that both Bowtell and Lockhart et al. teach probes which detect protein expression through RNA expression analysis. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Further regarding claim 122, Lockhart et al. and Bowtell do not specifically teach at least two probes complementary and hybridizable to genomic sequences contained entirely within an intron.

Regarding claim 122, Hui et al. teach intron probes, that is, probes that are complementary and hybridizable to genomic sequences contained within an intron, by teaching intron probes in general and specifically teaching probes/oligonucleotides which are complementary and hybridizable to intron regions of the genomic VHL suppressor gene (see column 3 lines 4-7 and note that the plural “probes” are taught and thus at least two probes are taught) which: “. . . can be immobilized as an array” (see column 10 lines 53 and 54). Hui et al. teach intron probes provide structural information which is crucial DNA sequence information:

“Methods for identifying VHL tumor suppressor gene mutations have been disclosed in the above noted publications and patent applications. While these methods have had some success in small scale sampling, as demonstrated in the above noted publications, they suffer from practical and theoretical shortcomings. In particular, nucleic acid assays, using cDNA sequences, cannot find mutations in the introns or at the intron/exon boundary of genomic DNA because convenient amplification of such regions requires at least one primer from within the region. Without having at least a small part of the intron amplified, it is impossible to obtain the crucial DNA sequence information by conventional means. Further, mRNA and cDNA are not necessarily the preferred molecules for diagnosis, if genomic DNA is available. This flows from the fact that intact mRNA is often difficult to obtain from patient samples, while genomic DNA sufficient for analysis can usually be obtained even from very small patient samples. Another shortcoming is that one of the most commonly used methods

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for diagnosing VHL tumor suppressor gene mutations, Southern blot probing, is time consuming and does not lend itself to use in a rapid or low cost diagnostic laboratory” (see column 2 lines 17-38);

“The instant invention provides a low cost, high sensitivity and high specificity methodology for routine diagnostic testing of VHL tumor suppressor gene mutations. It provides intron based primers and combinations of primers which simplify the work of the diagnostic technician” (see column 2 lines 59-65);

“It is a further object of the instant invention to provide oligonucleotides from intron regions of the genomic VHL tumor suppressor gene (at human chromosome 3p25-p26) that can be used for the diagnosis of VHL tumor suppressor gene mutation” (see column 3 lines 32-36).

Although this is a new rejection it is noted that Applicant argues that there would be no reason to combine the intron probes of Hui et al. with either the teachings of Bowtell or Lockhart et al. Applicant agrees that Lockhart et al. teach sequence signatures in array sbut then argues that this would not lead one of ordinary skill in the art to use intron probes in the arrays of Lockhart et al. Examiner respectfully disagrees. As already given above Lockhart et al. specifically teaches that probes may hybridize partial sequences which are sequence signatures and fragments of which an intron can be a specific example as disclosed by both Hui et al. as given above and Ashe et al. as

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follows. Thus and contrary to Applicant's argument, one of ordinary skill in the art would be motivated to combine the intron probes of Hui et al. and Ashe et al. in at least the arrays of Lockhart et al., as Lockhart generally teaches probes to partial sequences and both Hui et al. and Ashe et al. specifically teach intron probes which hybridize with partial gene sequences which are introns. Thus there is at least this motivation and reason to combine the teachings of the cited prior art. That Lockhart et al. do not exclude intron probes was a fact noted by Examiner and was not the sole basis for the claim rejection.

Applicant also argues that Hui et al. do not provide a motivation to combine their introns probes with other probes in the arrays of Lockhart et al. Again, Examiner respectfully disagrees. Hui et al. provide the motivation to use intron probes as provided below and above and the newly cited teaching of Ashe et al. also provide the same. As Lockhart et al. teach that a wide assortment of different probes can be used and generally teach the subgroup of probes which includes the intron probes of Hui et al. and Ashe et al., it would have been obvious from these teachings to use the intron probes of Hui et al. and Ash et al. in the arrays of Lockhart et al. as further given below.

Regarding claim 122, Ashe et al. also teach detection of genes in the gene structure of a plasmid using gene-specific intron probes specific (entire Article especially the last full paragraph on p. 2503 and Figure 9, noting the array of cells).

Further regarding claim 185, Ashe et al. specifically teach that probes are used which exclude the low information content of repetitive elements by teaching the DNA

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containing the *A/u* repeat is not used as a probe (see Figure 5 D and legend). It is noted that this teaching at least overcomes Applicants arguments regarding the lack of this teaching in Lockhart et al. However, Examiner still maintains that Lockhart et al. also provide this teaching as although the term “low information” is discussed with examples in the instant specification, “low information” is not defined and the low information teaching of Lockhart et al. is reasonably interpreted to be the low information content as recited in the claim.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the arrays of Lockhart et al. and Bowtell by including intron probes as suggested by both Hui et al. and Ashe et al. with a reasonable expectation of success. The motivation to do so is provided by Hui et al. who teach intron probes for gene detection and who teach that intron probes can be used for diagnosis, specifically diagnosis of the VHL tumor suppressor gene mutation (see column 3 lines 4-7). Further motivation to do so is provided by Ashe et al. who, as with Hui et al., teach intron probes and specifically teach that gene-specific intron probes can be used to detect a gene in a plasmid structure which is a type of gene structure. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

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7. Claim 223 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al., and Bowtell, Hui et al., and Ashe et al. as applied to claims 122 and 185 above, and further in view of Schena et al. (1996, previously cited).

Lockhart et al., and Bowtell, and Hui et al. teach as noted above.

Lockhart et al., and Bowtell, and Hui et al. do not teach wherein the organism is a plant.

Regarding claim 223, Ashe et al. suggest that intron probes can be used to measure incorporation of a second gene copy (see 1st sentence of 1st paragraph on p. 2506) but do not specifically teach intron probes for plant genomic sequences. However this teaching of Ashe et al. provides further motivation for arrays of probes including intron probes to detect plant genomic sequences.

Schena et al. teach microarrays to measure expression of plant genes (see 2nd paragraph of p. 10614).

Although this is a new rejection is noted that Applicant argues that Schena et al. only teach probes to cDNA and thus argues that probes to introns are not taught by Schena et al. However, Schena et al. broadly teach the analysis of complete genome sequences by probes which necessarily include introns (see 1st sentence on p. 10614). Additionally as given above, the teachings of Hui et al. and Ashe et al. are specifically relied upon for intron probes with Ashe et al. also suggesting probes to plant intron sequences, and the teachings of Schena et al. and not specifically relied upon for the teaching of intron probes.

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Lockhart et al., and Bowtell, and Hui et al. by targeting nucleotide sequences of plant genes as suggested by Schena et al. with a reasonable expectation of success. The motivation to do so is provided by Schena et al. who teach usefulness of microarrays in measuring plant genes and the teaching of Lockhart et al., and Bowtell, and Hui et al. who teach the detection of genes and gene mutations using arrays and microarrays. Further motivation to do so is provided by Ashe et al. who generally teach that plant genomic sequences should be analyzed in the same way as humans and *Drosophila*, which is a type of animal, and teach that intron probes can detect genes and their structure in animals (entire article, especially see last paragraph on p. 2506 continued to and through the next two full paragraphs on p. 2507). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Rejections Necessitated by Amendment

New Claim Rejection - 35 USC § 103

8. Claims 228-231 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (1997, previously cited), Bowtell (1999 previously cited), Hui et al. (United States Patent 6,013,436 filed August 19, 1996 and issued January 11, 2000), and Ashe et al. (1997, previously cited) as applied to claim 122 and 185 above, and further in view of Xing et al. (1993).

Lockhart et al., Bowtell, Hui et al., and Ashe et al. teach as noted above.

Regarding claims 228 and 230, Lockhart et al. further teach “The target polynucleotide whose sequence is to be determined can be isolated from a clone, a cDNA, genomic DNA, RNA, cultured cells, or a tissue sample”; and further teaches “If the target is mRNA, the sample is obtained from a tissue in which the mRNA is expressed” and “sufficient DNA is present in the tissue sample to dispense with the amplification step”, in other words the total cellular DNA, which is nucleic acid, is used (see column 21 lines 8-37 and entire reference). Thus Lockhart et al. at least suggest a sample comprising a population of mRNA.

Regarding claim 229, Lockhart et al. teach “The target can be labeled at one or more nucleotides during or after amplification” (see column 21 lines 33-34).

Regarding claim 231, Lockhart et al. teach an array with at least 10,000 different probes by teaching high density arrays of different probes, with probe density ranging from 625 to 10 million probes per 1 cm². (Fig. 2; col. 6, lines 62-67; col. 7).

Bowtell and Ashe et al. teach RNA but do not specifically teach that a sample population comprises mRNA.

Regarding claims 288 and 230, that intron probes for detection of mRNA in samples was well known at the time of the claimed invention is further shown by the teaching of Xing et al. Xing et al. teach intron probes for detection of mRNA (entire article, especially the Abstract and the second paragraph on p. 1327).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Lockhart et al., Bowtell, Hui et al., and Ashe et al. by using intron probes to detect mRNA or nucleic acid derived from mRNA as suggested by Xing et al. with a reasonable expectation of success. The motivation to do so is provided by Xing et al. who teach: “To investigate whether the concentrated RNA signals detected with genomic probes represented unprocessed transcripts, mature mRNA, or excised or excised introns, we performed in situ hybridization with intron-specific and cDNA probes” (see second paragraph on p. 1327). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Species Election

9. As the claims to elected species remain rejected, the claims to non-elected species are not examined.

Conclusion

10. No claim is free of the prior art.
11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples

/M. S./

Examiner, Art Unit 1637

December 5, 2009

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637